Baseline high levels of complement component 4 predict worse clinical outcome at 1-year follow-up in first-episode psychosis

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Background

Recent evidence has highlighted the potential role of complement component 4 (C4) in the development of schizophrenia. However, it remains unclear whether C4 is also relevant for clinical outcome and if it could be considered a possible therapeutic target.

Supporting the role of C4 in psychosis, Sekar et al have shown that the association of schizophrenia with variation in the Major Histocompatibility Complex locus (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) arises in substantial part from many structurally diverse alleles of the C4 gene (Sekar et al., 2016). A recent study also showed that schizophrenia risk-associated variants in the C4 locus are associated with increased complement neuronal deposition and synapse uptake which has been suggested as possible mechanism mediating the development of psychotic symptoms (Sellgren et al., 2019). We have previously reported alterations in the complement biomarkers in patients with first episode psychosis compared with healthy controls (Kopczynska et al., 2019) and another recent study has identified elevated levels of C4 in patients with chronic schizophrenia and in subjects at ultra-high risk of developing psychosis (Laskaris et al., 2019).

We have previously shown that other immune biomarkers, such as interleukin-6, interferon-γ and C reactive protein predict worse clinical outcome at 3-months or 1-year follow-ups in patients with first episode psychosis (Mondelli et al., 2015; Nettis et al., 2019), but no study so far has investigated the role of C4 in clinical outcome in psychosis. The aim of this study was to investigate whether baseline levels of C4 predict worse clinical outcome at 1-year follow-up in patients with first episode psychosis.

Methods

This is a naturalistic longitudinal study where n=25 patients with first episode psychosis were assessed at baseline (i.e. as soon as possible and within 3 months after the first contact with psychiatric services) and then followed-up prospectively for their clinical outcome at 1 year from baseline assessment. Patients were recruited as part of the Genetics and Psychosis (GAP) study and we refer to our previous publication for detailed information about recruitment and clinical assessment of the participants (Mondelli et al., 2015; Nettis et al., 2019). Severity of psychopathology at baseline was measured using the Positive and Negative Syndrome Scale (PANSS).

Information about clinical outcome at 1-year was obtained using the WHO Personal and Psychiatric History Schedule (PPHS) (WHO, 1995). Patients were defined as non-responders if they presented at 1-year follow-up with either continuous illness or with one or more relapses with personality change, while they were categorized as responders if they either met complete recovery or no relapses with residual personality changes or one or more relapses with no marked personality change. According to these criteria n=12 patients were classified as non-responders (mean±SEM age: 33.2±3.7 years, n=10 males) and n=13 as responders (age: 27.5± 1.8 years, n=9 males).

Baseline serum samples were aliquoted and stored at -80°C and not subjected to freeze-thaw until analyses. Concentrations of complement component 4 (C4) were measured using established in-house enzyme-linked immunosorbent assays (ELISA). Detailed procedure for analyses of C4 in this sample has been previously published (Kopczynska et al., 2019). C-

reactive protein (CRP) was measured using a commercial ELISA (CRP Duoset DY1707; R&D Systems, Abingdon, UK).

Data were analysed using the Statistical Package for Social Sciences version 24.0 (SPSS Inc., USA). ANCOVA analyses were conducted to investigate differences in baseline C4 levels between responders and non-responders at 1-year covarying for baseline severity of symptoms (total score of PANSS) and for level of C reactive protein. We then conducted Receiver Operating Characteristic (ROC) curve analyses to test the ability of C4 levels to correctly identify non-responders from responders.

Results

Non-responders show significantly higher baseline C4 levels compared with responders when controlling for baseline psychopathology and baseline levels of C reactive protein (552.5±31.3 vs 437.6±25.5 mcg/ml; p=0.008; see Figure 1). When investigating the ability of C4 levels to distinguish responders from non-responders, we found that the area under the ROC curve was 0.795 and the threshold point for C4 to distinguish between responders and non-responders appear to be around 490 mcg/ml (see Figure 2).

Figure 1: Box plots of C4 levels in Responders and Non-Responders, showing the distribution of the data based on the five summary numbers: minimum value, first quartile, media, third quartile, and maximum value.

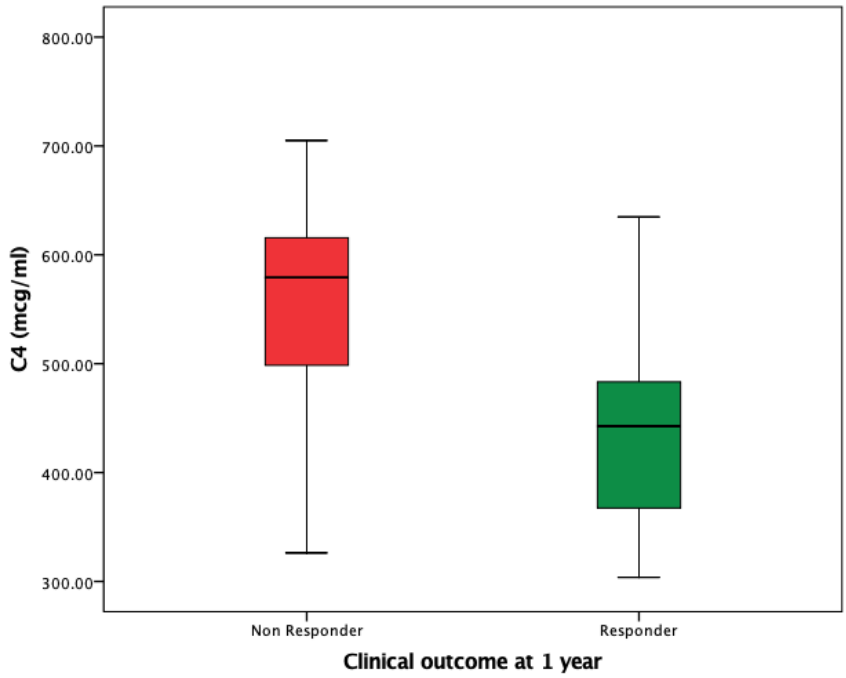
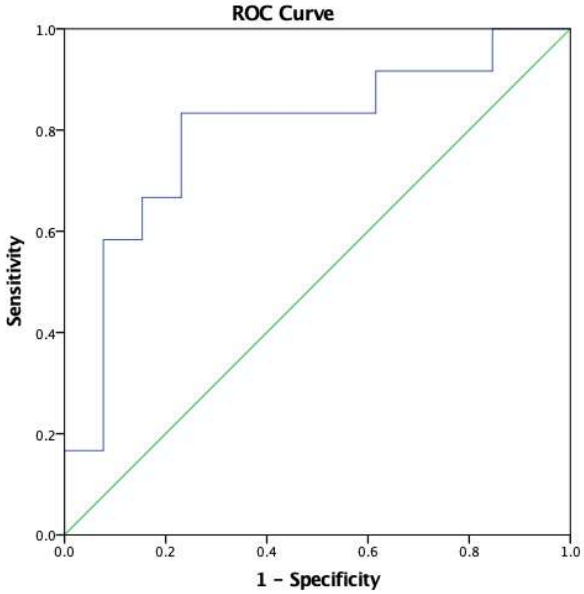


Figure 2: The ROC curve for levels of C4 predicting response to treatment



Discussion

Our findings show baseline C4 levels predict clinical outcome at 1-year follow-up in patients with first episode psychosis. The value of the area under ROC curve suggests baseline C4 levels could be a good biomarker to distinguish non-responders from responders. Interestingly the threshold at which C4 appears to distinguish responders from non-responders was found to be at 490 mcg/ml, which is just above what is considered to be normal range in clinical test (160-480 mcg/ml). Our findings suggest a possible a relevant clinical threshold for future studies testing the role of C4 in clinical outcome in psychosis.

The mechanisms through which increased C4 levels could contribute to worse clinical outcome may involve an excessive synaptic pruning induced by an increased C4 deposition at synaptic. Indeed, Sellgren et al, have recently shown that schizophrenia risk-associated variants within the human complement component 4 locus are associated with increased neuronal complement deposition and synapse uptake (Sellgren et al., 2019). Future studies would need to test the efficacy of possible therapeutic strategies targeting C4 or synaptic pruning as main hypothesised mechanism linking excess of C4 to worse clinical outcome.

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Conflict of interest

Prof Pariante and Dr Mondelli have received research funding from Johnson & Johnson as part of a research program on depression and inflammation. Prof Pariante has received research funding from the Medical Research Council (UK) and the Wellcome Trust for

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